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Osteochondrodysplasias in South Africa

Peter Beighton
Department of Human Genetics, University of Cape Town, South Africa

Jürgen Spranger's visit to the University of Cape Town in 1974 provided impetus for the establishment of a bone dysplasia registry. By 1996 more than 2,500 affected persons had been documented and radiographs and DNA had been obtained in many instances. Of these disorders, about 1,500 fall into the category of "osteochondrodysplasias" as listed in the International Nomenclature [Spranger, 1992].

The numbers of affected persons with each of these disorders are presented in this article. Departmental or collaborative investigations on DNA banked in conjunction with the registry, has resulted in localization or characterization of several determinant genes. In this way, Spranger's early contributions to the Cape have led directly to the elucidation of several import genetic skeletal dysplasias. © 1996 Wiley-Liss, Inc.

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INTRODUCTION

Jürgen Spranger made his first academic visit to the University of Cape Town in 1974. The Chair of Human Genetics had been established two years previously and a large number of patients with a wide variety of osteochondrodysplasias were available for investigation. Professor Spranger offered to see an unlimited number of patients or sets of radiographs; by the end of the first week, he had pronounced on more than 200 diagnostic problems and he then sought refuge on the beach. Nevertheless, his visit was highly successful and he astounded the local medical community with accurate diagnoses of exotic disorders such as parastremmatic dysplasia, acromesomelic dwarfism, and osteoglophonic dysplasia.

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Address reprint requests to Professor P. Beighton, Department of Human Genetics, Medical School, University of Cape Town, Observatory 7925, South Africa.

Dedicated to Jürgen W. Spranger on the occasion of his 65th birthday with admiration and best wishes.

Jürgen Spranger made several visits to Cape Town and gave impetus to the establishment of a skeletal dysplasia registry in this department. By 1996 more than 2,500 affected persons had been evaluated and documented; of these about 1,500 had the specific osteochondrodysplasias which form the subject of this article. In many instances radiographs repose in our archives, and DNA has been banked from numerous affected persons and their families. It has become apparent that several unique genetic skeletal disorders are present in South Africa, while other conditions which are common elsewhere are lacking. These discrepancies, which are probably the consequence of genetic mechanisms such as the founder effect and biological pressures, have considerable practical implications. In addition, the banked DNA represents an invaluable resource for molecular investigations.

The purpose of this article is to pay tribute to my long standing friend and colleague, Jürgen Spranger, to acknowledge his seminal role in the Cape Town skeletal dysplasia investigations, and to document the comparative frequency of the osteochondrodysplasias in this country.

MATERIALS AND METHODS

During the past 25 years regular genetic clinics have been held at the Groote Schuur Hospital, the Red Cross Children's Hospital and the Princess Alice Orthopaedic Hospital, Cape Town. In addition, an extensive programme of "out-reach" clinics is undertaken in peripheral areas throughout the former Cape Province. In an earlier phase, before other genetic centers became fully established in this country, intermittent clinics were held in many parts of South Africa. In particular, a regular skeletal disorder clinic, which was conducted at the Baragwanath Hospital, Johannesburg, represented a fruitful source of research material. In addition to the genetic clinics, diagnostic surveys have been conducted throughout the country at special schools and institutions for persons with physical handicap.

Clinical and genealogical data concerning every patient have been recorded on standardized proformata and, whenever possible, clinical photographs and radiographs have been obtained. In the latter context, the Spranger dictum has been followed: "Never attempt a diagnosis on a single film. Seven views, no more and no less are required (skull lateral, spine lateral, chest and shoulders pa, knee ap, elbow ap, hands, and wrists ap)."

Whenever necessary, members of the department were available to travel in order to investigate additional relatives and to obtain radiographs or blood specimens for further study. With the advent of molecular technology, emphasis has been given to DNA banking, and specimens from a large number of persons and families with diverse skeletal dysplasias are now kept in our laboratory. The clinical records and radiographs are maintained in the Department of Human Genetics and names and diagnoses on file are cross indexed in accordance with the format used by Professor VA McKusick at the Johns Hopkins Hospital, Baltimore, MD.

Osteochondrodysplasias, in which a firm diagnosis has been made, are listed in Table I, together with the numbers of affected persons, using the general format of the International Classification which was communicated by Spranger [1992]. In many instances relatives were affected but these persons have been included only when they have been evaluated and documented. If investigations of a listed condition have resulted in publication, a recent or key reference is provided. For the sake of brevity, the MPS group of disorders and related metabolic conditions have been excluded from this review. In the same way, dysostoses in which only a section of the skeleton is affected, and malformation syndromes which involve tissues other than the bones, have also been omitted, apart from a few which are of special importance in this country (Table II). Conditions in which departmental or collaborative molecular investigations have led to gene localization or characterization, or in which molecular studies are currently underway, are indicated by asterisks in the tables. A few of the listed osteochondrodysplasias occur with a uniquely high frequency in South Africa. In view of their practical significance and their implications for gene localization and characterization studies, brief overviews of these disorders are provided.

Sclerosteosis

Sclerosteosis is a severe autosomal recessive disorder in which marked skeletal overgrowth leads to gigantism and asymmetrical overgrowth of the mandible, with facial palsy and deafness due to cranial nerve entrapment. Progressive increase in the diameter of the calvarium may occur in adulthood [Beighton, 1988] and lead to elevation of intracranial pressure and sudden death from impaction of the brain in the foramen magnum. Sclerosteosis resembles the van Buchem form of

TABLE I. Osteochondrodysplasias Studied in South Africa

Disorder	Number of patients seen	Reference
Thanatophoric dysplasia	15	Beighton et al., 1994
Achondroplasia[a]	109	Beighton and Bathfield, 1981
Hypochondroplasia	21	Heselson et al., 1979
Achondrogenesis	9	Beighton and Cremin, 1974
Metatropic dysplasia	5	
Short rib dysplasia	2	
Asphyxiating thoracic dysplasia	7	
Ellis-van Creveld dysplasia	2	
Atelosteogenesis	4	
Diastrophic dysplasia	8	
Dyssegmental dysplasia	1	
Kniest dysplasia	2	
Stickler dysplasia[a]	12	
Hypochondrogenesis	2	
Spondyloepiphyseal dysplasia congenita[a]	47	Ramesar and Beighton, 1992
Namaqualand hip dysplasia[a]	55	Sher, 1991
Beukes hip dysplasia[a]	51	Beighton et al., 1994
Dyggve-Melchior-Clausen dysplasia	2	Beighton, 1990
Pseudoachondroplasia	46	Heselson et al., 1977
Spondylo-epimetaphyseal dysplasia	11	
Spondylo-epimetaphyseal dysplasia with joint laxity (SEMDJL)[a]	22	Beighton, 1994
Spondylo-metaphyseal dysplasia	20	Kozlowski et al., 1980
Multiple epiphyseal dysplasia[a]	42	
Chondrodysplasia punctata (various types)	12	Heselson et al., 1978
Metaphyseal dysplasia - Schmid type	2	
Metaphyseal dysplasia - McKusick type	2	
Metaphyseal dysplasia - Shwachman type	1	
Brachyolmia[a]	2	Gardner and Beighton, 1994
Dyschondrosteosis	7	Goldblatt et al., 1987
Langer mesomelic dysplasia	1	Beighton, 1974
Acromesomelic dysplasia	4	Goldblatt and Smart, 1986
Tricho-rhino-phalangeal dysplasia	4	
Pseudohypoparathyroidism	5	
Cleidocranial dysplasia[a]	55	
Osteodysplasty	3	
Campomelic dysplasia	5	
Kyphomelic dysplasia	2	Viljoen and Beighton, 1988
Boomerang dysplasia	1	Winship et al., 1990

(*continued on next page*)

endosteal hyperostosis but is more severe and has the additional feature of syndactyly, usually of the second and third fingers [Beighton et al., 1984].

Sclerosteosis has been identified in more than 80 members of the Afrikaner community of South Africa with a gene frequency in excess of 1%; there are more than 10,000 asymptomatic heterozygotes in this population. As the Afrikaners are of Dutch stock, and as van Buchem disease is virtually confined to Holland, it seems likely that the two conditions are the consequence of homozygosity for the same, as yet undetermined, gene fault and that the phenotypical discrepancies may be the result of the action of epistatic influences.

Spondyloepimetaphyseal Dysplasia With Joint Laxity (SEMDJL)

SEMDJL is an autosomal recessive dwarfing skeletal dysplasia in which widespread bony changes are associated with ligamentous laxity. Affected infants may have dislocated hip joints and radial heads, with talipes equinovarus and spinal malalignment. A characteristic facial appearance and variable structural cardiac defects complete the phenotype. The sequelae of articular laxity are difficult to treat and progressive kyphoscoliosis may lead to paraplegia and death from cardio-respiratory embarrassment. Survival into adulthood is unusual [Beighton, 1994]. The condition has been recognized in about 25 children in the Afrikaner population and genealogical investigations have revealed ancestral links with persons of Germanic stock.

Osteogenesis Imperfecta Type III (OI-III)

Osteogenesis imperfecta type III is characterized by a severe fracturing tendency, stunted stature, white sclerae, and autosomal recessive inheritance. Although OI-III is generally rare, it is comparatively common in the indigenous Black population of South Africa. *More* than 100 affected children have been identified in this group and it is evident that the heterozygote frequency is high. It is uncertain whether this situation is the consequence of a founder effect or whether there is, or has been, some unrecognized biological advantage in heterozygosity [Viljoen and Beighton, 1987].

COMMENT

Jürgen Spranger prompted the early endeavours in this department in the field of syndrome delineation

TABLE I. (*continued*)

Disorder	Number of patients seen	Reference
Osteogenesis imperfecta I[a]	142	Beighton et al., 1983
Osteogenesis imperfecta II	26	Spranger et al., 1982
Osteogenesis imperfecta III[a]	102	Viljoen and Beighton, 1987
Osteogenesis imperfecta unclassifiable	71	Beighton et al., 1988
Osteoporosis with pseudoglioma[a]	2	
Idiopathic juvenile osteoporosis	2	
Bruck syndrome	2	Viljoen et al., 1989
Geroderma osteodysplastica	1	
Parastremmatic dysplasia	1	Horan and Beighton, 1976
Hypophosphataemic rickets	21	
Osteopetrosis, precocious, AR	6	Horan and Beighton, 1978
Osteopetrosis delayed, AD[a]	20	Beighton et al., 1979
Osteopetrosis intermediate, AR	6	Beighton et al., 1977
Pycnodysostosis	12	
Osteopoikilosis	3	
Melorheostosis	5	
Osteopathia striata with cranial sclerosis	3	Horan and Beighton, 1978
Camurati-Engelmann syndrome	2	
Sclerosteosis[a]	81	Beighton, 1988
Van Buchem disease	0	Beighton et al., 1984
Craniometaphyseal dysplasia[a]	14	
Fronto-metaphyseal dysplasia	2	Beighton and Hamersma, 1980
Pyle disease	2	Beighton, 1978
Osteoectasia with hyperphosphatasia	1	
Oculo-dento-osseous dysplasia, severe type	2	Beighton et al., 1979
Dysplasia epiphysealis hemimelica	7	
Multiple cartilaginous exostoses	10	
Enchondromatosis, Ollier	8	
Enchondromatosis, Maffucci	2	
Spondyloenchondromatosis	2	Zack and Beighton, 1995
Osteoglophonic dysplasia	1	Beighton, 1989
Fibrous dysplasia (Jaffe-Lichtenstein)	20	
Fibrous dysplasia with precocious puberty	1	
Cherubism	1	
Idiopathic osteolysis, phalangeal	1	
Idiopathic osteolysis, carpo/tarsal	1	
Undiagnosable osteochondrodysplasias	86	

[a]Conditions in which departmental or collaborative molecular investigations have led to gene localization or categorization, or in which molecular studies are underway.

TABLE II. Other Important Skeletal Disorders in South Africa

Schwartz syndrome	10	Viljoen and Beighton, 1992
Gaucher disease, non-neuropathic	112	Goldblatt and Beighton, 1979
Blount disease	181	Bathfield and Beighton, 1978
Ectrodactyly	71	Viljoen and Beighton, 1984
Marfan syndrome	41	Viljoen and Beighton, 1990
Radial ray defects	38	Cox et al., 1989
Fibrodysplasia ossificans progressiva	10	Connor and Beighton, 1982

and subsequently, by virtue of his interest in OI, in the biochemical and molecular basis of the inherited collagen disorders. In turn, these studies led to DNA banking in a variety of conditions and the development of projects aimed at gene localization and characterization. In particular, in the three severe autosomal recessive disorders which are outlined above, recognition of the underlying molecular abnormality would facilitate carrier detection and antenatal diagnosis. Genomic screening is under way but so far the gene loci have not been identified.

History has a tendency to repeat itself, and it is significant that Jürgen's son, Dr. M. Spranger, visited this department in 1988. In the short time that he was in the Cape, he followed in his father's footsteps and investigated a large kindred with an unusual segregation of ectrodactyly [Spranger and Schapera, 1988]. Perhaps a third generation will one day continue the family tradition!

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